Chidhood AML: Is It Difficult To Cure? King Fahd Specialist Hospital Damman Experience

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Abstract: Acute myeloid leukemia (AML) is a heterogeneous disease that accounts for approximately 20% of acute leukemias in children and adolescents. Despite the lack of targeted therapy for most subtypes, survival rates have reached approximately 60% for children treated on clinical trials in developed countries. Most of the advances have been accomplished by better risk classification, the implementation of excellent supportive care measures, adaptation of therapy on the basis of each patient's response to therapy, and improvements in allogeneic hematopoietic stem cell transplantation (HST). However, it is unlikely that further gains can be made through these measures alone. The identification of molecular abnormalities that are potential targets of new therapies is expected to pose much impact on the treatment outcomes of the disease. The development of molecularly targeted agents holds great promise for the future as well. The present study reports the King Fahd Specialist Hospital-Dammam (KFSH-D) experience in the management of pediatric AML patients who referred to the hemato-oncology department starting from May 2008 until September 2012 as well as the result of their follow up.
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1. Introduction:

Acute myeloid leukemia (AML), a heterogeneous group of diseases that can be classified by morphology, lineage, and genetics, shows variable responses to the same therapy. This heterogeneity reflects the diversity of myeloid precursors that are susceptible to malignant transformation and the assortment of genetic events that can lead to this transformation [1]. Most subtypes of AML are characterized by subpopulations of leukemic stem cells, or leukemia-initiating cells that have an unlimited self-renewal capacity and an organization similar to that of normal hematopoietic cells. AML comprises nearly a quarter of childhood acute leukemias [2]. Biologic and clinical similarities exist among AML in children, adolescents, and young adults.

Despite substantial progress in the management of childhood acute myeloid leukemia, only about 50% of patients are cured by intensive chemotherapy [3]. The treatment of AML has been considerably modified over the years. Therapeutic trials have shown that intensified induction and consolidation chemotherapy improves the outcome in AML. According to published results, event-free survival (EFS) will end up at 50% of children with AML and overall survival (OS) figures of 60–65% have been obtained [4-7].

Despite the large number of subtypes and the lack of targeted therapy for most subtypes, the treatment outcome is considered to have improved markedly for children with AML. Such an improvement is attributed to excellent supportive care, adaptation of therapy on the basis of each patient's response, and the use of intensive chemotherapy or hematopoietic stem cell transplantation (HSCT) [8]. The treatment outcome achieved on the multi-institutional AML02 trial is similar to that reported by the Medical Research Council (MRC) [9], the Nordic Society for Pediatric Hematology and Oncology (NOPHO) [10], the Berlin-Frankfurt-Muenster study group (BFM) [11], the Japanese Childhood AML Cooperative Group [12] and the Children's Oncology Group (COG) [13]. However, the cure rates for some subtypes of childhood AML remain unacceptably low, and novel therapies are needed.

The aim of this study is to report the incidence of pediatric AML is King Fahd Specialist Hospital-Dammam (KFSH-D) and to correlate our treatment protocol outcome with their clinico-pathologic manifestations and laboratory prognostic factors such as cytogenetics and flow cytometric markers.

2. Patients and Methods:

The pediatric age at KFSH- Dammam is set at 0-17 years.Ninety one cases of acute leukemia in

pediatric patients were seen between May 2008 and September 2012, thirty cases were AML. Thirty pediatric AML patients were enrolled in this study and who represented the total number of pediatric AML patients referred to KFSH-D from May 2008 until September 2012. All patients were assessed at diagnosis for the presence of lymhadenopathy, splenomegaly, hepatomegaly, gum hypertrophy, cholorma, leukemia cutis, petichae, bleeding and CNS manifestations. Patients were diagnosed to have AML on morphologic and cytochemical examination of bone marrow aspirate Leishman stained slides, and further classified according to the FAB system. Immunophenotyping was done onBD FACS Canto II instrument, Diva software. The following panel of markers was applied:

Tube #	FITC	PE	PerCP	APC
1	IgG	IgG	CD45	IgG
2	CD14	CD11c	CD45	CD20
3	CD3	CD8	CD45	CD4
4	CD34	CD10	CD45	CD19
5	CD7	CD33	CD45	CD56
6	CD15	CD117	CD45	CD22
7	CD38	CD13	CD45	CD11b
8	CD66c	CD2	CD45	CD5
9	CD64	CD58	CD19	HLA-DR
10	MPO	CD79a	cCD3	CD45
11	TdT		CD45	cCD22
12	cy IgG	cy IgG	cy IgG	CD45

Cytogenetic study, in the form of conventional karyotyping or FISH, was done for 21 patients. Molecular study for abnormal fusion genes was done for 12 patients.

Patients received chemotherapy in the form of:

MRC12 (modified):

Induction Course 1: ADE

ADE 10+3+5: Ara-C 100mg/m^2 12-h i.v. d 1–10; Daunorubicin 50 mg/m^2 i.v. d 1, 3, 5; Etoposide 100mg/m^2 i.v. d 1–5

Course 2: ADE 8+3+5: Ara-C reduced to 8 days.

Consolidation

Course 3: Cytosine Arabinoside 1.5 g/m^2 12-hourly by 4 hour I.V. infusion on days 1, 3 and 5 (6 doses).

Course 4: Cytosine Arabinoside 1.5 g/m^2 12-hourly by 4 hour I.V. infusion on days 1, 3 and 5 (6 doses).

High-dose Ara-C (3.0 g/m^2)

Course 3: Cytosine Arabinoside 3.0 g/m^2 12-hourly by 4 hour I.V. infusion on days 1, 3 and 5 (6 doses).

Course 4: Cytosine Arabinoside 3.0 g/m^2 12-hourly by 4 hour I.V. infusion on days 1, 3 and 5 (6 doses).

Plus Etoposide 100 mg/m^2 d 1–5 for for COG AML 0531 which was used for few patients. Figures 1 and 2 demonstrate POG AML and MRC12 treatment protocol schema.

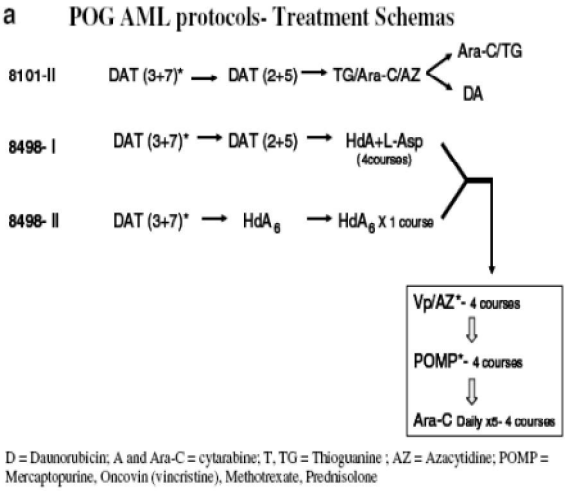

Figure (1): Schematic diagram of POG AML treatment protocol

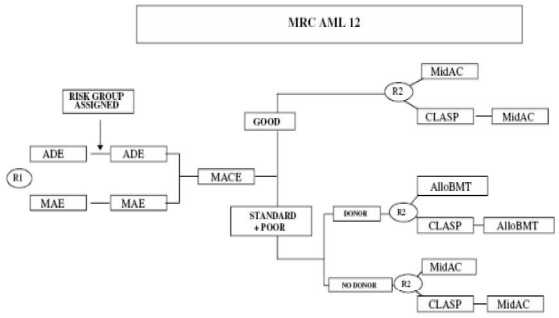

Figure (2): Schematic diagram of MRC12 treatment protocol

Analysis of data was done using the SPSS package version 18. For numerical data, parametric data were expressed as mean, standard deviation and range, while non-parametric data were expressed as median and interquartile range. Qualitative data were expressed as frequency and percentage. Chi-square test or Fisher's exact test were used to examine the relation between qualitative variables. Non-parametric numerical data were analyzed using Mann-Whitney test. Correlation analysis was performed by Spearman's rank correlation. Kaplan Meir curves were applied for overall and disease free survival. A *p*-value less than 0.05 was considered significant.

3.Results:

Thirty pediatric AML patients were enrolled in this study. They were 15 males and 15 females with M:F ratio of 1:1. Patients' age ranged from 1 to 17 years with a median of 9.5 and a mean of 8.75±5.247

years. Figure (1) shows the demographic distribution of the referred cases.

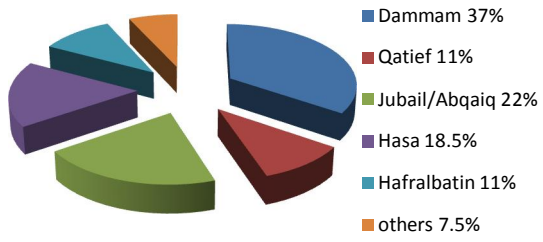

Fig (3) Geographic distribution of referred pediatric AML patients

Clinical manifestations:

13.3% of the patient complained of weight loss, 43.3% had history of bleeding, 33.3% complained of fatigue, 86.7% of patients complained of bone pains, 70% complained of fever, and 36.7% of patients complained of poor appetite. On examination 66.7% of the patients had pallor, 60% had organomegaly, 50% had lymphadenopathy, 23.3% had gum hypertrophy, and 13.3% had CNS manifestations. Chloroma was present in 6.7% and leukemia cutis in 3.7% of the patients. 23.3% had infection and 13.3% had DIC.

Laboratory findings showed that 13.3% of patients had a total leukocytic count (TLC) of more than $100x10^9$/L and 10% had a count of >50 and $<100x10^9$/L. Only 4 patients (13%) had platelet count (PLT) $<20x10^9$/L. Only 1 patient (3.73%) had positive infiltration of the CSF. The incidence of tumor lysis syndrome (TLS) in our AML patients was 0%. None of our patients had renal impairment at the diagnosis.22% of patients had hepatic dysfunction at diagnosis. Figure (2) shows the different FAB types of the patients.

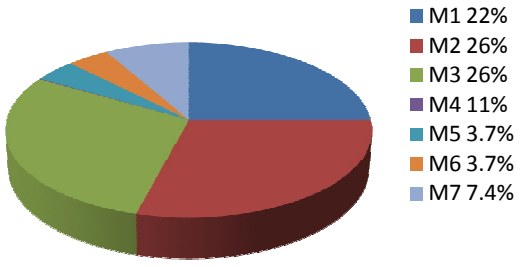

Figure (4): Percentage of the different AML FAB subtypes

TLC ranged from 1.1 to 344 with a median of 27.45 and a mean of $49\pm55.788X10^9$/L. Hb ranged from 5.8 to 11.9 with a median of 8.35 and a mean of 7.96±2.27 gm/dl. PLT ranged from 12 to 302 with a median of 40.5 and a mean of $63.47\pm63.48X10^9$/L. Bone marrow blast percentage ranged from 0 to 92 with a median of 58 and a mean of 50.27±33.23%.

On flow cytometric examination, 56.7% of patients were CD34 positive, 53.3% were MPO positive, 60% were HLA-DR %, 90% were CD33 positive, 80% were CD13 positive, 76.7% were CD117 positive 40% were cd38 positive, 23.3% were CD56 positive and 26.7% expressed monocytic markers.

Cytogenetic examination revealed that 6 patients had normal karyotype, 14 patients (46.7%) had favorable cytogenetics, where 6 patients had t(8;21), 5 patients had t(15;17),1 patient had RARarearrangment, and 3 patients had inv. 16. 6 patients (20%) had unfavorablecytogenetics, where 2 patients had -7, and 1 patient had each of the following translocations: (7;12), t(11;19), t(10;11), and t(9;11). 1 patient had intermediate risk cytogenetics in the form of trisomy 8 and 2 patients had Down's syndrome with trisomy 21, clones with other cytogenetic markers were present in both. 1 patient had Fanconi's Anemia and 1 patient had secondary AML. Positive molecular studies were obtained in 17 out of 28patients tested (60%). 6 patients had ETO/AML1 gene, 5 patients had PML/RARA gene, 1 had other RARA gene mutation, 1 patient had MLL fusion gene, 3 patients had inv (16).FLT3-ITD was detected in 1 patient and FLT3-D835 variant was detected in a patient with t (15;17).

Twenty nine patients (96.6%) were treated in KFSHD and 1 was transferred to another center. 20patients (66.6%) were treated with chemotherapy (16 patients were on MRC12, 8 patients were on PETHEMA, 2 patients were on FLAx2 and 1 patient was on each of the POG 8498, the Japanese protocol (DS), the Bfm 98 and MRC15). 10 patients (33.3%) were treated with chemotherapy + Stem Cell Transplantation "SCT" (9 allogeneic and 1 autologous).All APL (AML-M3)patients were treated with chemotherapy except 1 who had been treated with chemotherapy+ allogenic SCT after relapse.All relapsed patients were treated with FLA+/- G-CSF as second line and Clofarabine + Ara-C as second line.

At end of induction 24patients (82.7%) were in remission and 5 (17.2%) patients did not achieve remission. Complications of chemotherapy included bleeding (33%), myelo-suppression (56.7%), infection (80%) and other complications (6.7%)such as cardiomyopathy, renal impairment and hyperglycemia.

Out of the 29 patients treated at our hospital, 7 patients (23.3%) are dead, 19 patients (63.3%) are still alive, and 4 patients (13.3%) are lost to follow up. 17

patients (56.7%) achieved complete remission,6patients achieved partial remission. 9 patients (30%) had disease relapse (7 had 1 relapse and 2 had 2 relapses).

Figure 5 demonstrates the causes of death in our patients.Figures 6 and 7 show the overall and the disease free survival of the patients. Figures 8 and 9 shows the overall survival in 2 years. Figure 10 shows the probability of overall survival in 5 months (49.9%).

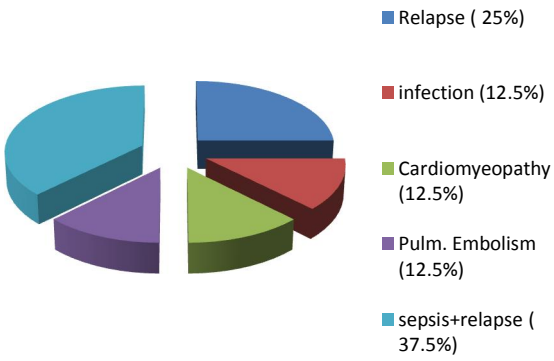

Figure (5): Causes of death in our patients

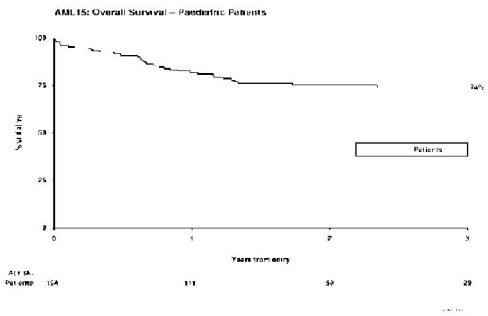

Figure (6): Overall survival of the patients

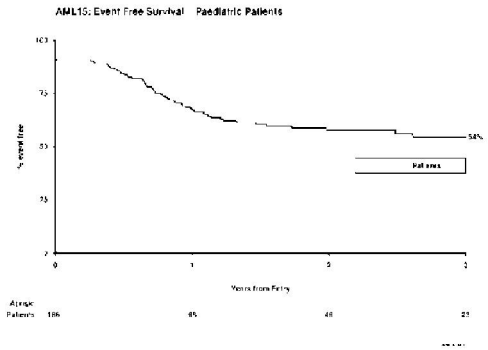

Figure (7): Event free survival of the patients

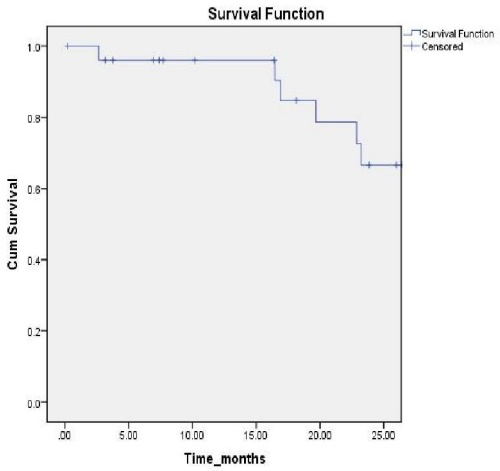

Figure (8): Overall survival in two years

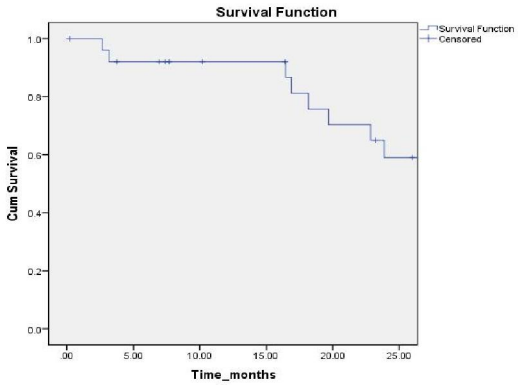

Figure (9): Event free survival in two years

There was no association between chromosomal abnormalities and either of sex, response to induction therapy, DIC, CNS manifestations, infection, lymphadenopathy, organomegaly, or either of the flow cytometric markers except for HLA-DR (p=0.037). Chromosomal abnormalities were associated with myelo-suppression (p=0.044). Response to induction therapy was not associated with any of the clinic-pathologic or the laboratory parameters.

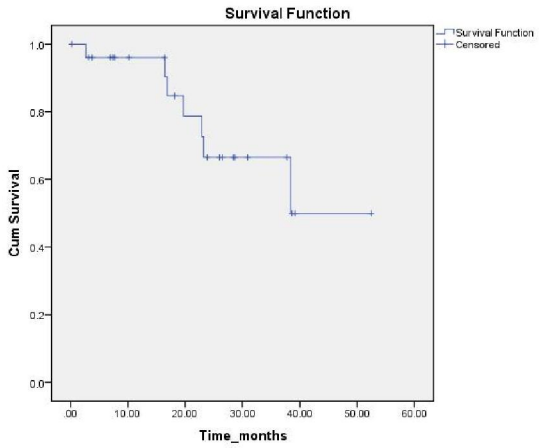

Figure (10): Probability of overall survival in 50 months (OS=49.9%)

4.Discussion:

Acute myeloid leukemia has posed significanttherapeutic challenges to pediatric oncologists. Despite intensive therapy, half of the children with AML relapse and die from their disease. Efforts to identifyrisk factors in AML are directed toward defining populations who may benefit from alternative therapies. Patients at lower risk for relapse may benefitfrom treatment de-escalation, sparing them adverseside effects. Management of high-risk patients mayprove more difficult, as the nearly myeloablative nature of AML therapy leaves little room for therapy escalation short of stem cell transplantation [14]. Prognostic factors include host factors "such as gender, age, race, and constitutional abnormalities", response to therapy "such as response to induction therapy, multi drug resistance and relapse", as well as disease characteristics "such as TLC, platelet count, FAB classification, cytogenetic and molecular abnormalities" [15].

These factors are generally interdependent, the sum of which ultimately determines disease response and patient outcome. In addition, prognostic factors may change as treatment changes, thusnecessitating the evaluation of all established and putativeprognostic markers within the framework of a defined therapy [16]. 13.3% of our patients had a total leukocytic count of more than $100x10^9$/L, and 13% had a platelet count of less than $20x10^9$/L, a thing considered to be of bad prognostic implication. However, we failed to find a significant association between those two variables and either of chromosomal abnormalities or response to induction therapy, in contrast to results reported by other studies [15, 16], most probably due to the small number of patients.

Because morphologic disease response has been shown to be such a powerful prognostic factor, the role of disease persistence below detection at the morphologic level (MRD) has been evaluated as a prognostic factor in AML. More than 80% of pediatric patients with AML who undergo induction therapy achieve complete remission (CR),as assessed by morphologic evaluation of the marrow at the end of induction therapy. However, nearly half of these patients are destined for relapse and poor outcome. Identification of occult disease in patients in morphologic remission may identify patients at high risk for impending relapse [17]. Appropriate intervention in this group of patients could potentially prevent morphologic relapse, and there should be adequate time from the detection of MRD to morphologic relapse to allow for intervention [18]. In our study, MRD was detected in 10 (33.3%) of our patients, of whom 6 died (1 post relapse and the other after partial remission). 4 patients had partial remission and 2 relapsed.

Diagnostic cytogenetics is widely recognized as one of the most significant prognostic factors in AML. Informative cytogeneticsis usually available in 70%–80% of pediatric patients with AML, and clonal abnormalities are demonstrated in nearly 70% of those with informative cytogenetics [19]. The prognostic significance of karyotypic abnormalities has been evaluated in several trials, and specific favorable and unfavorable subgroups of AML have been identified [20].

Identification of subpopulations within AML for treatment stratification is likely to play increasingly important role in future therapeutic strategies. APL is now proved to be a unique subgroup of AML with very specific therapy requirements in both children and adults. The results of our study reveal that the overall survival and the event free survival of patients of APL having the characteristic t(15;17) and the PML/RARA fusion gene and patients having the t(8;21) and the ETO/AML1 fusion gene was higher than those harboring unfavorable cytogenetics. We agree in our results with other reported studies [19-22].

Other data reported in literature are also emerging that particular morphologic or cytogenetic subgroups may respond differently to specific therapies [23, 24].

Given the nature of AML therapy, HST may be the only available short-term option for therapy intensification in high-risk patients, and because most patients do not have matched family donors for transplantation, the use of matched unrelated donor (URD) transplantation needs to be considered in patients without family donors. Given that HST, especially from a URD, carries significant short- and long-term toxicities, its utility in high-risk patients must therefore be carefully examined. However, if

patients at high risk for relapse do not receive an HSCT during CR1, there is a high chance that they will relapse and will need a transplant as therapy after relapse if they achieve a second CR. Thus, the option for these patients may not be whether they should receive an HST, but whether they should be transplanted in first. Similarly, for patients with prognostic features placing them in a good risk category, the use of HST from matched family donors remains controversial [25].

Several cooperative groups, including the MRC and BFM, have concluded that patients with good-risk AML can be effectively treated with only chemotherapy and that allogeneic HSCT should be reserved for patients who relapse[26]. This approach depends on the ability tore-induce a remission as well as the effectiveness of HST in this group of patients. North American studies have demonstrated that the best relapse-free and overall survival for pediatric patients with AML is achieved in those receiving family donor HST in CR1, except for patients with inv(16) [27].

In our study 10 patients (33.3%) underwent BMT, all of whom achieved remission except for one patient, who relapsed with 50% blasts in the marrow. Only two of the transplanted patients had favorable cytogenetics in the form of inv (16) and t(8;21), one had intermediate cytogenetics in the form of trisomy 8 and the rest had unfavorable cytogenetics. We agree in our results with Burnett et al. and Woods et al. [27, 28].

In conclusion, the most important objective in the treatment of pediatric AML is to improve the outcome with the least toxicity. Managing patients who are at extremely high risk for relapse is difficult. Prognostic markers for relapse should be prospectively studied and validated in large multi-institutional trials. Once validated, such markers should be acted upon, and a relapse threshold and survival after relapse must be established. Patients harboring particular markers putting them below an accepted threshold would be promptly referred for HST hoping to improve their outcome. Studies should be also directed toward therapeutically exploiting such prognostic factors. The development of targeted therapies that will both reduce the leukemic burden and also eliminate or control the leukemic stem cell population is expected to be of great value for achieving improved outcomes for AML patients. As these therapies are developed to target specific characterizing the different subtypes of AML, the role of HST will hopefully decrease. This hope would be applicable for children and adults with both high-risk as well as good-risk AML.

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